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Articles

(WOMEN AND) CHILDREN FIRST: APPLICABLE TO LIFEBOATS? APPLICABLE TO HUMAN EXPERIMENTATION?

LAINIE FRIEDMAN ROSS, M.D., PH.D.* AND M. JUSTIN COFFEY, B.A.**

I. INTRODUCTION

The phrase “women and children first” refers to the rescue policy on a sinking ship. Its origin is credited to the brave action of Lieutenant-Colonel Alexander Seton and his men on the HMS Birkenhead.¹ On February 26, 1852, the HMS Birkenhead hit a rock just off Danger Point near southern Africa that tore its metal hull. Those soldiers who did not drown in their sleep rushed on deck and attempted to free the lifeboats. Three lifeboats were released, and the women and children were ushered onto them. As the ship began to sink, Captain Seton drew his sword and ordered his men to stand fast because he feared that if the men rushed the lifeboats, the women and children might perish. Over two-thirds of the men died.²

To a pediatrician (LFR), it seems obvious why we would want to rescue children first. They are our future, our greatest resource. But why save the women? It may have been a show of chivalry, or that naval etiquette requires sailors to place passenger well-being before their own, particularly in times of peace. Alternatively, one could argue that the children needed caregivers, and that in 1852, it seemed obvious to bring the women along. Today, given the increasing role of men as primary caregivers, that may not be as justified.³

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1. Anonymous, *A Ship Tradition: Women and Children First*, at http://ne.essortment.com/shiptraditionw_rrqb.htm (last visited Sept. 10, 2002).

2. *Id.*

3. See Deborah Sharp, *Custody Clash Reflects Parent’s Changing Roles*, USA TODAY, July 28, 1999, at 5A (nearly 19% of the nation’s 10.3 million preschool children were cared for primarily by their father in 1994 compared with 14% in 1977); U.S. DEP’T COMMERCE, U.S. CENSUS BUREAU REP., GROWTH IN SINGLE FATHERS OUTPACES GROWTH IN SINGLE MOTHERS, Dec. 11, 1998, available at <http://www.census.gov> (last visited Sept. 15, 2002).

Until 1990, in contrast, the medical research priority was the opposite: Women and children last. The justification was paternalistic: Women and children needed protection. But with this protection came a drawback: The health issues unique to women and children were understudied and under-funded.⁴ In 1990, the Office of Research on Women's Health (ORWH) was established to ensure that "women's health research is part of the scientific framework at the NIH and throughout the scientific community."⁵ The NIH began to require the participation of women in NIH-supported research, or a justification for their exclusion.⁶ The moral justification is simple: If competent adults have the right to decide for themselves what risks they are willing to bear for particular benefits, then this holds for both competent men and competent women. The exclusion of women from the frontlines of medical research cannot be morally justified.

The first U.S. guidelines regarding children in research were published in the late 1970s and early 1980s⁷ and were based on the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) report published in 1977.⁸ The National Commission recommended that, "whenever possible, research involving risk should be conducted first on animals and adult humans in order to ascertain the degree of risk and the likelihood of generating useful knowledge."⁹ Sometimes this is not relevant or possible, as when the research is designed to study disorders or functions that have no parallel in animals or adults. However, in June 1996, the American Academy of Pediatrics (AAP) and the National Institute of Child Health and Human Development (NICHD) sponsored a workshop entitled the "Inclusion of Children in Clinical Research",¹⁰ the theme of which was that current policy may be too little, too late.¹¹ The policies of the late 1990s reflect this perspective.

4. See, e.g., Gina Kolata, *NIH Neglects Women, Study Says*, N.Y. TIMES, June 19, 1990, at C6; Claude Bennett, *Inclusion of Women in Clinical Trials-Policies for Population Subgroups*, 329 NEW ENG. J. MED. 299 (1993); Cary P. Gross et al., *The Relation Between Funding by the National Institutes of Health and the Burden of Disease*, 340 NEW ENG. J. MED. 1881 (1991).

5. NIH, OFFICE OF RESEARCH ON WOMEN'S HEALTH, COMMEMORATING A DECADE OF PROGRESS, available at <http://www.4.nih.gov> (last visited Sept. 14, 2002).

6. *Id.*

7. Protection of Human Research Subjects: Proposed Regulations on Research Involving Children, 45 C.F.R. § 46 (1978); Additional Protections for Children Involved as Subjects in Research, 45 C.F.R. § 46.401 (1983).

8. NAT'L COMM'N, PUB. NO. (OS) 77-0004, REPORT AND RECOMMENDATIONS: RESEARCH INVOLVING CHILDREN (1977).

9. *Id.* at 3-4.

10. NICHD, Inclusion of Children in Clinical Research Workshop (June, 1996) (on file with author).

11. Council on Pediatric Research, AAP, Meeting the Research Needs of Children and Youth: Research Along the Life Cycle (unpublished manuscript, on file with author).

In 1997, the Food and Drug Administration Modernization Act (FDAMA) was passed.¹² The Act gives pharmaceutical manufacturers an additional six months of exclusivity if they perform drug testing in children. In 1998, the Food and Drug Administration (FDA) published final rules that require manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients.¹³ In 1998, the NIH also issued a new policy to increase the enrollment of children in NIH-funded research.¹⁴

While we support a policy of “children first” on sinking ships, in this paper, we will argue that the new initiatives place too much emphasis on access and not enough emphasis on protection. In medical research, a more appropriate policy may be to leave children last.¹⁵

II. CHILDREN IN RESEARCH: A BRIEF HISTORY

A quick look at the history of pediatric experimentation finds that it is largely one of child abuse.¹⁶ For example, immunization research often enrolls children-subjects because they are more likely to be disease naïve.¹⁷ Historically, researchers often chose a convenient sample: the researcher’s children, servants, or slaves.¹⁸ Children could also be recruited from institutions. Alfred Hess, medical director of the Hebrew Infant Asylum in New York City, explained the scientific advantage of enrolling institutionalized children: it permitted “conditions which are insisted on in considering the course of experimental infection among laboratory animals, but which can rarely be controlled in a study of infection in man.”¹⁹ Children were also “cheap” in the sense of non-valued; in fact, one researcher explained that he used children-subjects because they were “cheaper than calves.”²⁰

12. See FDAMA of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

13. 21 C.F.R. §§ 201, 312, 314, 601 (1998).

14. NIH, POL’Y AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RES. INVOLVING HUM. SUBJECTS, *available at* <http://grants.nih.gov> (last visited Sept. 14, 2002).

15. See Harry Shirkey, Editorial Comment, *Therapeutic Orphans*, 72 J. PEDIATRICS 119 (1968). We want to assert our support for pediatric research, but only want to question how and when such research is done. The exclusion of children from research would harm children as a class and leave them as “therapeutic orphans.” This phrase was coined by Dr. Harry Shirkey to express his frustration with the lack of financial support by government and industry for pediatric drug investigation when most of the laws empowering the FDA to regulate drugs were passed in response to drug-induced adverse effects in the pediatric population.

16. Susan E. Lederer & Michael A. Grodin, *Historical Overview: Pediatric Experimentation, in* CHILDREN AS RES. SUBJECTS: SCI., ETHICS & L. 19 (Michael A. Grodin & Leonard H. Glantz eds., 1994).

17. *Id.* at 4.

18. *Id.*

19. *Id.* at 6; see also Alfred F. Hess, *The Use of a Series of Vaccines in the Prophylaxis and Treatment of an Epidemic of Pertussis*, 63 JAMA 1007 (1914).

20. Lederer & Grodin, *supra* note 16, at 12.

Protection of human subjects came to international focus with the documented abuses of research subjects by the Nazis.²¹ The Nuremberg Code, the first international code of research ethics, was adopted in 1946 and explicitly stated that "the voluntary consent of the human subject is absolutely essential."²² There was no mention of proxy consent; the subject had to be able to consent to participate. Literally interpreted, this would have prohibited the participation of children and any other incompetent persons in all medical research. Later codes of ethics included the possibility of participation by incompetent subjects by permitting proxy consent.²³

In a seminal article published in the *New England Journal of Medicine* in 1966, Henry Beecher described 22 unethical experiments that had been performed and published in the past two decades, four of which involved children.²⁴ His point was to provoke the research community to comply with the Nuremberg Code. It is in this ambience that the National Commission was formed. The National Commission issued its first report regarding the protection of children-subjects in 1977,²⁵ and the protection of human subjects more generally in the Belmont Report in 1978.²⁶ The National Commission's report on children stated that children are an especially vulnerable population because they cannot consent for themselves. They suggested that research should be done first on animals, then, when possible and appropriate, on adult humans, then on older children, and finally on younger children.²⁷

III. GUIDELINES FOR CHILDREN IN RESEARCH

Most of the National Commission's recommendations were incorporated into the federal regulations for the protection of human research subjects.²⁸ Subpart D of the regulations provides additional protections for children involved as subjects in research,²⁹ and focuses on the concepts of risk and risk/benefit. Risk is

21. Nuremberg Code, Principle 1 (1946), available at <http://ohsr.od.nih.gov> (last visited Sept. 14, 2002); see also *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Law No. 10*, Vol. II (U.S. Gov't Printing Office, 1948).

22. *Id.*

23. WORLD MED. ASS'N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MED. RES. INVOLVING HUM. SUBJECTS, available at http://www.wma.net/e/policy/17-c_e.html (last visited Sept. 15, 2002) (as adopted by the 18th WORLD MED. ASS'N, Helsinki, Finland, 1964; and amended by, 29th-Tokyo, Japan, 1975; 35th-Venice, Italy, 1983; 41st-Hong Kong, China, 1989; 48th-Somerset West, Republic of South Africa, 1996; and, 52nd-Edinburgh, Scotland, 2000) [hereinafter WORLD MED. ASS'N].

24. Henry K. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1354 (1966).

25. See NAT'L COMM'N, *supra* note 8 and accompanying text.

26. NAT'L COMM'N, PUB. NO. (OS) 78-0012-014, BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUM. SUBJECTS OF RES. (1977).

27. NAT'L COMM'N, *supra* note 8, at 2.

28. 45 C.F.R. § 46.101 (1991).

29. 45 C.F.R. § 46.401 (1983).

classified as "minimal," "a minor increase over minimal risk," or "more than a minor increase over minimal risk."³⁰ "Minimal risk" is defined in the federal regulations as: "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."³¹ No definition is given for either a minor increase or more than a minor increase in either Subpart A, Subpart D, or the National Commission's reports. Rather, the National Commission stated that in its determination of risk and harm the institutional review board (IRB) should:

"[C]onsider the degree of risk presented by the research from at least the following four perspectives: a common-sense estimation of risk; an estimation based upon the investigators' experience with similar interventions or procedures; any statistical information that is available regarding such interventions or procedures; and the situation of the proposed subjects."³²

Such imprecision may be necessary to make the regulations usable, yet, there is a striking divergence of opinions regarding what research is characterized as "minimal risk," and what is characterized as "more than minimal risk."³³ This fact is important because how risk is classified determines what else is necessary to ensure that the risk/benefit is morally justifiable in pediatric research.³⁴ For example, a child's dissent can be overridden if the research offers the prospect of a direct therapeutic benefit.³⁵ Alternatively, if the research entails more than a minor increase over minimal risk but does not offer a direct therapeutic benefit, it must present an opportunity to prevent or alleviate serious health problems and requires national review.³⁶

The emphasis of the new policies implemented by the FDA and NIH in the 1990s has shifted from protecting children from research risks to ensuring access for children. Two reasons for the policy changes were 1) the concern of the pediatric community that many pharmaceuticals and therapies prescribed to

30. 45 C.F.R. § 46.405 (1983).

31. 45 C.F.R. § 46.102 (2001).

32. NAT'L COMM'N, *supra* note 8, at 8-9.

33. Jeffrey Janofsky & Barbara Starfield, *Assessment of Risk in Research on Children*, 98 J. PEDIATRICS 842, 834 (1981).

34. Ross A. Thompson, *Vulnerability in Research: A Developmental Perspective on Research Risk*, 61 CHILD DEV. 1, 1-6 (1990); Terrence F. Ackerman, *Moral Duties of Investigators Toward Sick Children*, 3 IRB: A REV. OF HUM. SUBJECTS RES. 1, 2-4 (1981).

35. 45 C.F.R. § 46.405 (1983).

36. *See id.* § 46.407.

children had never been tested in children,³⁷ and 2) the FDA's response to the politicization of drug testing and approval by AIDS activists.³⁸ The activists successfully challenged a system that they deemed was too slow by securing passage of an accelerated approval process.³⁹ Some of the concerns raised by the activists regarding drug testing and approval are magnified in the pediatric population because of the lag time between FDA-approval of new drugs (often based solely on adult trials) and the initiation of clinical trials in children.⁴⁰

In 1994, the FDA published a final rule regarding specific requirements on content and format of pediatric labeling for human prescription drugs.⁴¹ The rule was an attempt to improve pediatric labeling by requiring drug manufacturers to survey existing data and determine whether those data were sufficient to support additional pediatric use information in the labeling of their drugs. The response was disappointing and did not substantially increase the pediatric use information for marketed drugs and biological products. Approximately 430 drugs and biologic supplements were submitted, of which 75% did not improve pediatric use information.⁴² More than half simply requested the addition, "[s]afety and effectiveness in pediatric patients have not been established."⁴³

The Pediatric Rule was proposed in 1997, finalized in 1998, and became effective on April 1, 1999.⁴⁴ It required manufacturers of certain new drugs and biological products to conduct studies to provide adequate pediatric labeling. After the FDA issued the proposed Pediatric Rule, but before the rule was finalized, Congress enacted FDAMA.⁴⁵ It provides economic incentives for conducting pediatric studies. According to a January 2001 status report to Congress, FDAMA

37. AAP COMM. ON DRUGS, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 95 PEDIATRICS 286 (1995).

38. Sharon Begley et al., *Desperation Drugs, Frustrated AIDS Patients Are Spurring the FDA to Relax the Rules of the Game*, NEWSWEEK, Aug. 7, 1989, at 48, 51; see also Stephen Jay Gould, *AIDS and FDA Drug-Approval Policy: An Evolving Controversy*, 2 J. HEALTH SOC. POL'Y 39 (1990); see generally RANDY SHILTS, *AND THE BAND PLAYED ON: POLITICS, PEOPLE, AND THE AIDS EPIDEMIC* (1987).

39. 21 C.F.R. §§ 314, 601 (1992).

40. See Regulations Requiring Manufacturer to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66, 632-33 (1998). See also 21 C.F.R. §§ 201, 312, 314, 601 (1998).

41. 21 C.F.R. § 201 (1994).

42. See *id.*

43. See Regulations, *supra* note 40, at 66,632.

44. See *supra* note 13. On October 17, 2002, the Pediatric Rule was struck down by the U.S. Court of Appeals for the District of Columbia on grounds that it exceeded the FDA's statutory authority. See Ass'n of Am. Physicians and Surgeons, Inc., et al., v. U.S. FDA, et al., No. CIVA.00-02898, 2002 WL 31323411 (D.D.C. Oct. 17, 2002). Although an appeal is likely, there is also an attempt to get Congress to pass legislation to codify the Rule. See Press Release, Louis Z. Cooper, M.D., AAP President, FDA Pediatric Rule Court Decision and Next Steps for Congress, (Oct. 18, 2002) (on file with the Journal of Health Care Law & Policy).

45. 111 Stat. 2296.

has been highly effective in generating pediatric studies on many drugs, although some categories of drugs and some age groups remain inadequately studied.⁴⁶ In January of 2002, FDAMA was reauthorized as the Best Pharmaceuticals for Children Act (BPCA) to continue to improve the safety and efficacy of pharmaceuticals for children.⁴⁷

The NIH also issued a new policy in 1998 to increase the enrollment of children.⁴⁸ All NIH-funded research must now include a plan for the inclusion of children, unless there is good justification to exclude them. To ensure that researchers comply, the NIH clearly stated on its Frequently Asked Questions (FAQ) webpage that the exclusion of children may affect the priority score given to determine grant funding.⁴⁹

Thus, the new policies encourage the inclusion of children in research, often earlier in the research process. This may be in conflict with the National Commission's second recommendation that research on children should proceed, when possible, only after testing on animals and human adults.⁵⁰ The change reflects different assumptions and beliefs regarding the risks and benefits of clinical research. While the historical concern was that justice required that subjects be recruited to share the burdens of risk, now the focus is on ensuring equity in subject recruitment to share the benefits. Are we misfocused?

IV. ASTHMA: A CASE STUDY

We will use the example of asthma to examine why the shift towards including children in clinical trials raises ethical concerns. One of us (LFR) first became sensitized to the serious problem in pediatric asthma studies after reading a letter to the editor in the *Journal of Pediatrics* by Dr. Ferdman from the Children's Hospital of Los Angeles and Dr. Church from the University of Southern California School of Medicine published in February 1999.⁵¹ Ferdman and Church commented on a study published in June 1998 by Shapiro et al. that found a dose-related effect of inhaled budesonide powder, an anti-inflammatory medication, in

46. DEP'T OF HEALTH & HUM. SERVICES, FDA, THE PEDIATRIC EXCLUSIVITY PROVISION: STATUS REP. TO CONGRESS (Jan. 2001), available at <http://www.fda.gov> (last visited Sept. 15, 2002).

47. BCPA, Pub. L. No. 107-109, 115 Stat. 1408 (2002), available at <http://thomas.loc.gov> (last visited Sept. 12, 2002).

48. See NIH policy, *supra* note 14.

49. NIH, OFFICE OF EXTRAMURAL RESEARCH, QUESTIONS AND ANSWERS ABOUT THE NIH GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS (1999), available at <http://grants.nih.gov> (on file with the Journal of Health Care Law & Policy).

50. See NAT'L COMM'N, *supra* note 8, at 2-5.

51. Ronald M. Ferdman & Joseph A. Church, *Ethical Issues of Placebo-Controlled Trials*, 134 J. PEDIATRICS 251, 251 (1999).

children with moderate to severe asthma.⁵² Ferdman and Church did not question the findings, only the methodology. They asked why a placebo group was included in addition to the three different arms of budesonide, given that current guidelines require anti-inflammatory medications for all individuals with moderate to severe asthma.⁵³ They argued that the trial put a large number of children at unnecessary risk as indicated by the fact that 44% of the placebo group withdrew from the study compared with 15-18% in the three budesonide groups and that withdrawals were mainly due to worsening asthma.⁵⁴

Shapiro responded that their study was critical because it was studying the safety and efficacy of a new mode of delivery, the turbuhaler, and that a placebo-controlled study was necessary for FDA approval.⁵⁵ They viewed the study as an ethical compromise in that they accomplished this protocol without incurring serious consequences in their subjects.⁵⁶ Shapiro's response failed scientifically and ethically. Scientifically, the researchers could have used active controls.⁵⁷ Ethically, the justification failed because, as Beecher noted two decades earlier, a study must be ethical at its inception, not in retrospect.⁵⁸ Thus, the fact that none of the subjects was seriously harmed is not sufficient to justify the researcher's methodology.

A brief background about asthma is important as a framework for the discussion of children as research subjects in clinical asthma trials. Asthma is one of the most common chronic diseases in the United States and its prevalence has been increasing since 1980.⁵⁹ In 1997, a total of 26.7 million persons reported a physician diagnosis of asthma during their lifetime.⁶⁰ Asthma is a lung disease with the following characteristics: 1) airway obstruction that is reversible either spontaneously or with treatment; 2) airway inflammation; and 3) increased airway responsiveness to a variety of stimuli.⁶¹ In the U.S. pediatric population alone,

52. See generally Gail Shapiro et al., *Dose-Related Efficacy of Budesonide Administered Via a Dry Powder Inhaler in the Treatment of Children with Moderate to Severe Persistent Asthma*, 132 J. PEDIATRICS 976 (1998).

53. NIH, NAT'L HEART, LUNG & BLOOD INS'T (NHLBI), GLOBAL STRATEGY FOR ASTHMA MGMT. & PREVENTION (1995) (NIH PUB. NO. 95-3659, 1995); see *supra* note 51.

54. Ferdman & Church, *supra* note 51.

55. Gail Shapiro, *Reply*, 134 J. PEDIATRICS 251, 251 (1999).

56. *Id.* at 252.

57. The FDA prefers placebo-controlled studies, although active controls can be used. See BARUCH A. BRODY, ETHICAL ISSUES IN DRUG TESTING, APPROVAL AND PRICING 105 (1995) (providing an extensive discussion of the FDA and placebos).

58. Beecher, *supra* note 24, at 1360.

59. David M. Mannino et al., *CDC Surveillance Summaries: Surveillance for Asthma – United States 1980-1999*, 51 MORBIDITY & MORTALITY WEEKLY REP. 1, 2 (2002), available at <http://www.cdc.gov> (last visited Sept. 30, 2002).

60. *Id.*

61. NIH, NHLBI, NAT'L ASTHMA EDUC. & PREVENTION PROGRAM, PUB. NO. 91-3042, EXPERT PANEL REP.: GUIDELINES FOR THE DIAGNOSIS & MGMT OF ASTHMA (1991) [hereinafter NIH GUIDELINES].

asthma affects about 5 million children,⁶² although there is evidence to suggest that a significant number of children with asthma remain undiagnosed.⁶³ Although life-threatening attacks are more common in those with severe disease, children with all degrees of asthma can have a life-threatening event. In 1998, asthma in children accounted for 5.8 million outpatient visits,⁶⁴ over 867,000 emergency department visits,⁶⁵ 174,000 hospitalizations,⁶⁶ and over 200 deaths.⁶⁷

In 1990, the U.S. Department of Health and Human Services (DHHS) made the reduction of asthma morbidity a national health care objective.⁶⁸ To that end, in 1991 the National Heart, Lung, and Blood Institute (NHLBI), a branch of the National Institutes of Health, published its *Guidelines for the Diagnosis and Management of Asthma* in an effort to achieve improved asthma care outcomes and to “bridge the gap between research and practice.”⁶⁹ These guidelines emphasized the importance of environmental control, objective lung function measurements, patient education, and the use of anti-inflammatory medications.⁷⁰ Specifically, the guidelines established inhaled corticosteroids (ICS) as primary therapy for moderate and severe asthma in adults and for severe asthma in children.⁷¹ In children with moderate asthma, the nonsteroidal anti-inflammatory drug cromolyn was considered first line therapy, and ICS were to supplement or replace cromolyn if symptoms persisted. The guidelines did state, however, that ICS “is an acceptable primary therapy for moderate asthma although a trial of cromolyn should usually precede its use because of the extensive clinical experience with

62. AM. ACADEMY OF ALLERGY, ASTHMA & IMMUNOLOGY, PEDIATRIC ASTHMA: PROMOTING BEST PRACTICE, GUIDE FOR MANAGING ASTHMA IN CHILDREN (1999), available at <http://www.aaaai.org> (last visited Sept. 15, 2002).

63. See generally Ellen F. Crain et al., *An Estimate of the Prevalence of Asthma and Wheezing Among Inner City Children*, 94 PEDIATRICS 356 (1994); see also Christine L.M. Joseph et al., *Prevalence of Possible Undiagnosed Asthma and Associated Morbidity Among Urban School Children*, 129 J. PEDIATRICS 735 (1996).

64. CDC, NAT'L CENTER FOR HEALTH STATISTICS, NEW ASTHMA ESTIMATES: TRACKING PREVALENCE, HEALTH CARE, AND MORTALITY: FACT SHEET, available at <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm> (last visited Oct. 24, 2002) (on file with the Journal of Health Care Law & Policy).

65. *Id.*

66. *Id.*

67. CDC, NAT'L CENTER FOR HEALTH STATISTICS, PUB. NO. 91-50212, NAT'L HOSPITAL DISCHARGE SURV.: ANNUAL SUMM. (1995); Vital & Health Statistics Series 13, No. 133 (1995)), available at <http://www.cdc.gov> (on file with the Journal of Health Care Law & Policy).

68. DHHS, PUB. NO. 91-50212, HEALTHY PEOPLE 2000: NAT'L HEALTH PROMOTION AND DISEASE OBJECTIVES (1990); see also DHHS, HEALTHY PEOPLE 2010 (2000), available at <http://www.cdc.gov/nchs/about/otheract/hpdata2010/about.htm> (last visited Sept. 15, 2002).

69. See NIH GUIDELINES, *supra* note 61, at Foreword.

70. See Beecher, *supra* note 24, at 1360.

71. *Id.*

and study of cromolyn sodium.”⁷² These recommendations are similar to the international pediatric asthma guidelines published in 1989,⁷³ 1990,⁷⁴ and 1992.⁷⁵

In 1995, the NHLBI in conjunction with the World Health Organization (WHO) jointly produced a report entitled *Global Initiative for Asthma*.⁷⁶ These guidelines revised the current classification of asthma to include both mild intermittent asthma and mild persistent asthma, and they recommended that children and adults with moderate persistent asthma be treated with ICS.⁷⁷ Adults, children, and infants with mild persistent asthma could be treated with either ICS or cromoglycate.⁷⁸ In 1997, the NHLBI issued revised guidelines that recommended ICS as first-line therapy for children and adults with mild persistent asthma.⁷⁹ It is important to note that these guidelines were established using data accumulated since the 1970s regarding the efficacy and safety of ICS in children,⁸⁰ especially overseas.⁸¹ In addition, researchers began to recognize that airway inflammation was a critical aspect of the pathology of asthma,⁸² and that ICS could prevent or reverse the inflammation.⁸³

72. See NIH GUIDELINES, *supra* note 61, at 81.

73. See generally J.O. Warner et al., *Management of Asthma: A Consensus Statement*, 64 ARCHIVES OF DISEASE IN CHILDHOOD 1065 (1989).

74. See generally Frederick E. Hargreave et al., *The Assessment and Treatment of Asthma: A Conference Report*, 85 J. ALLERGY & CLINICAL IMMUNOLOGY 1098 (1990).

75. See generally J.O. Warner et al., *Asthma: A Follow Up Statement from an International Pediatric Asthma Consensus Group*, 67 ARCHIVES OF DISEASE IN CHILDHOOD 240 (1992).

76. NHLBI, NIH, PUB. NO. 96-3659, A ASTHMA MANAGEMENT AND PREVENTION: A PRACTICAL GUIDE FOR PUBLIC HEALTH OFFICIALS AND HEALTH CARE PROFESSIONALS (1995), available at <http://www.ginasthma.com> (last visited Sept. 15, 2002) [hereinafter NHLBI].

77. *Id.* at 19-20 (Figures 10a and 10b).

78. *Id.*

79. NAT'L HEART, LUNG AND BLOOD INST., NIH, PUB. NO. 97-4051, Expert Panel Report 2: Guidelines for the Diagnosis and Mgmt. of Asthma, (1997), available at <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf> (last visited Sept. 15, 2002). Of note is that the 2002 NHLBI guidelines continue to recommend ICS as primary therapy for children and adults with mild persistent, moderate, and severe asthma. NHLBI, NIH, PUB. NO. 97-4051, Expert Panel Report 2: Guidelines for the Diagnosis and Mgmt. of Asthma-Update on Selected Topics 2002, available at <http://www.nhlbi.nih.gov/guidelines/asthma/execsumm.pdf> (last visited Nov. 25, 2002).

80. See, e.g., Simon Godfrey, *The Place of a New Aerosol Steroid, Beclomethasone Dipropionate, in the Management of Childhood Asthma*, 22 PEDIATRIC CLINICS OF N. AM. 147 (1975); S.P. Clissold & R.C. Heel, *Budesonide: A Preliminary Review of its Pharmacodynamic Properties and Therapeutic Efficacy in Asthma and Rhinitis*, 28 DRUGS 485 (1984); see also B. Davies, *A Comparison of Beclomethasone Dipropionate and Budesonide in the Treatment of Asthma*, 47 BRIT. J. CLINICAL PHARMACOLOGY 87, 87 (1993). The latter article provides that “critically assesses the published literature from 1980 to August, 1992.” *Id.*

81. The issue of whether the data is from U.S. studies or from overseas is relevant because of the need for FDA approval, and whether the FDA will accept studies conducted outside of the U.S. See BRODY, *supra* note 57, at 106-07.

82. Peter J. Barnes, *A New Approach to the Treatment of Asthma*, 321 NEW ENG. J. MED. 1517, 1517 (1989). The evidence can be found in K.F. Chung & S.R. Durham, *Asthma as an Inflammatory Disease: Clinical Perspective*, 48 BRIT. MED. BULL. 179 (1992).

83. Peter J. Barnes, *Inhaled Glucocorticoids for Asthma*, 332 NEW ENG. J. MED. 868, 868 (1995).

ICS were initially introduced to reduce the need for oral glucocorticosteroids in patients with severe asthma because chronic use of systemic glucocorticosteroids is associated with serious morbidity.⁸⁴ It was hypothesized that ICS would produce fewer systemic effects, and the early evidence supported this hypothesis.⁸⁵ As researchers recognized the inflammatory nature of asthma and the safety of ICS, there was a move to test ICS on individuals with less severe asthma.⁸⁶ Concerns of safety led to greater conservatism in pediatrics and explain in part why the 1991 guidelines recommended ICS for adults and children with severe asthma but only for adults with moderate asthma.⁸⁷ The guidelines recommended that children with moderate asthma begin with a trial of cromolyn and switch to ICS only if they do not get full symptomatic relief. It was expected that cromolyn would be effective in 60-80% of children with mild and moderate asthma.⁸⁸ Although guidelines were modified to support the use of ICS in 1995, prescribing patterns in the United Kingdom (U.K.) reveal a much higher use of ICS in children in the early 1990s than would be expected if it were only used when cromolyn failed.⁸⁹ This change is more likely due to physician belief in the superiority of ICS and greater ease in administration (once or twice a day versus four times a day).⁹⁰

The guidelines then are consistent with a children last philosophy. Despite mounting evidence of the safety of ICS in adults and children with moderate to severe asthma, concerns about long-term safety led scientists to be more conservative with pediatric recommendations.

The danger of such a philosophy, however, is also apparent. Although safety and efficacy of ICS were not completely established in 1991, physicians were

84. These side effects include suppression of the hypothalamic-pituitary-adrenal axis which can reduce adrenal response to stress, reduction in bone mass causing osteoporosis and an increased risk of vertebral and rib fractures, stunting of growth, thinning of the skin, easy bruising, cataracts, and psychiatric disturbance including emotional lability, aggressiveness and insomnia. *See id.* at 871-73. *See also* Soren Pedersen & Paul O'Byrne, *A Comparison of the Efficacy and Safety of Inhaled Corticosteroids in Asthma*, 52 (Suppl. 39) ALLERGY 1, 16-27 (1997).

85. The main side effects of long-term ICS are oral thrush, sore throat and hoarseness. *See* R.N. Brogden et al., *Beclomethasone Dipropionate: A Reappraisal of its Pharmacodynamic Properties and Therapeutic Efficacy After a Decade of Use in Asthma and Rhinitis*, 28 DRUGS 99, 121 (1984).

86. *See, e.g.*, W.B. Chambers & V.A. Malfitan, *Beclomethasone Dipropionate Aerosol in the Treatment of Asthma in Steroid-Independent Children*, 7 J. INT'L MED. RESEARCH 415 (1979); Clissold & Heel, *supra* note 80, at 505; Sture Lorentzson et al., *Use of Inhaled Corticosteroids in Patients with Mild Asthma*, 45 THORAX 733 (1990).

87. NIH GUIDELINES, *supra* note 61, at 81.

88. Shirley Murphy & H. William Kelly, *Cromolyn Sodium: A Review of Mechanisms and Clinical Use in Asthma*, 21 DRUG INTELLIGENCE AND CLINICAL PHARMACY 22, 28 (1987). Murphy and Kelly cite several studies that report a success rate between 60% and 80%. *Id.*

89. *See also* R.J. Kaarsgaren et al., *Asthma Medication in Children—1991*, 88 RESPIRATORY MED. 383, 385 (1994); J.O. Warner, *Review of Prescribed Treatment for Children with Asthma in 1990*, 311 BRIT. MED. J. 663, 665 (1995).

90. A.W. Robins & B.W. Lloyd, *Most Consultants Deviate from Asthma Guidelines*, 311 BRIT. MED. J. 508, 508-09 (1995); Warner, *supra* note 89, at 665.

already using ICS with children despite the fact that children (or certain classes of children) might have had a different risk/benefit from the medication than adults. In retrospect, ICS have been found to be effective and to have minimal side effects in children, but that has not always been the case when extrapolating information about children from adult data.⁹¹

V. BEECHER REVISITED: ASTHMA RESEARCH BETWEEN 1998-2000

The question that the Ferdman and Church letter raised for LFR was whether the Shapiro et al. study was an aberration or whether it was typical of asthma research, particularly among asthma research done here in the U.S. We focused on U.S. research because although all developed countries are signatories to the Declaration of Helsinki and the research ethics guidelines it imposes, each country also has its own research ethics guidelines and research review processes, both of which may influence the methodology used.

We performed an online search using MedLine, a medical journal search engine, and found 57 original prospective full-length articles of clinical asthma trials in the U.S. that included children-subjects published between January 1, 1998, and December 30, 2000. A full methodology and the research findings are described elsewhere.⁹² In this paper, we want to discuss two findings that are consistent with the new policies regarding children in research. First, nearly 75% (42/57) of the asthma studies reviewed were placebo-controlled. Second, approximately 72% (41/57) involved both children and adults. We will address whether such study designs are ethical and what purpose the enrollment of children served. Additionally, we will suggest reasons for the designs of these studies.

VI. THE USE OF PLACEBOS IN ASTHMA RESEARCH

Placebo-controlled studies have been the "gold standard" of research since their introduction half a century ago.⁹³ A study is placebo-controlled if it compares

91. See the examples cited by the FDA. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, Part V, Proposed Rule, 62 Fed. Reg. 43901, 43903 (proposed July 24, 1997) (to be codified at 21 C.F.R. §§ 201, 312, 314, and 601).

92. M. Justin Coffey, *The Ethics of Placebos in Pediatric Research: Asthma as a Case Study* (2002) (unpublished B.A. thesis, University of Chicago) (on file with the author).

93. The first placebo-controlled trial was probably conducted in 1908 when W.H.R. Rivers compared alcohol and other drugs to an inert substance (not then referred to as a placebo) in their effects on fatigue. ARTHUR K. SHAPIRO & ELAINE SHAPIRO, *THE POWERFUL PLACEBO* 137 (1997). The first *randomized* placebo-controlled trial to be conducted was a study of immunization against whooping cough done under the auspices of the Medical Research Council (U.K.). Medical Research Council Whooping-Cough Immunization Committee, *The Prevention of Whooping Cough by Vaccination*, 1951 BRIT. MED. J. 1463, 1464 (1951). With the publication of classic papers by Wolf, Beecher, and others, the placebo control became an integral part of the randomized controlled trial. See

an experimental drug with an inert substance. It is a randomized controlled trial if the therapy given to the subject is chosen randomly and not by the physician-scientist. Randomized controlled trials are usually done in a double-blind fashion; neither the researcher nor the subject knows to which arm the subject is randomly allocated.

Placebo-controlled studies can be ethical. In fact, in 1977, the AAP Committee on Drugs offered five conditions in which the use of placebos is ethical in drug research in children: 1) when there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process; 2) when the commonly used therapy for the condition is of questionable or low efficacy; 3) when the commonly used therapy for the condition carries with it a high frequency of unacceptable side effects; 4) when the incidence and severity of undesirable side effects produced by adding a new treatment to an established regimen are uncertain; and 5) when the disease process is characterized by frequent spontaneous exacerbations and remissions.⁹⁴ These conditions were reaffirmed by the AAP in 1995.⁹⁵

The first condition states that placebo-controlled trials are ethical when there is no standard of care and it is not clear that the new intervention is effective. In these cases, it is unknown whether the experimental drug is better than placebo. Such uncertainty at the beginning of a trial is known as clinical equipoise.⁹⁶ However, by 1991, there was a standard of care for children with asthma, as clearly stated in several consensus statements.⁹⁷ The guidelines recommended that all children with moderate or severe asthma be given a daily anti-inflammatory of cromolyn or ICS respectively. And yet, 32 of the 42 asthma studies involving placebos published in the years 1998-2000 compared the study drug to placebo. That is, in at least one of the arms, subjects were either discontinued from their current treatment or not begun on an anti-inflammatory agent despite the consensus for anti-inflammatories. All such studies, then, were unethical because 1) they failed to provide standard of care in the placebo-arm;⁹⁸ and 2) they lacked

generally Stewart Wolf, *The Pharmacology of Placebos*, 2 PHARMACOLOGY REV. 689 (1959); Henry K. Beecher, *The Powerful Placebo*, 159 JAMA 1602 (1955).

94. AAP COMM. ON DRUGS, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 60 PEDIATRICS 91, 99 (1977).

95. AAP, *supra* note 37, at 294.

96. The term equipoise was coined by Charles Fried to refer to the state of uncertainty that must exist for a clinical trial to be justified. CHARLES FRIED, MEDICAL EXPERIMENTATION: PERSONAL INTEGRITY AND SOCIAL POLICY 52-53 (North-Holland 1974). Benjamin Freedman suggested that the equipoise needed for a clinical trial to be ethical is "clinical equipoise," which refers to a state of disagreement in the expert community about the merits of a particular therapy. Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 NEW ENG. J. MED. 141, 144 (1987).

97. See, e.g., NIH, *supra* note 61, at 79-84; Warner, *supra* note 73; and Hargreave, *supra* note 74.

98. Not all ethicists would agree that all placebo-controlled trials are unethical when a standard of care exists. See, e.g., BRODY, *supra* note 57, at 112-13, 116. Brody argues that if three criteria are met, placebo-controlled trials can be ethical in the face of a proven therapy: "(1) withholding the proven

equipoise at the start of the trials. As one researcher admitted: "Asthma symptoms would be expected to worsen in the placebo group during the treatment period because these patients were dependent on inhaled steroids but were not allowed treatment with inhaled steroids while in the study."⁹⁹

A second way that placebo-controlled studies can be ethical is if they compare a new study drug as an add-on (condition 4). In an add-on study, subjects continue to take their current treatment and are given an additional drug (or placebo) to see if the new drug improves their well-being. To be ethical, add-on studies require that the subjects' current treatment conform to standard of care. In other words, if one wanted to study the effectiveness of montelukast, a leukotriene inhibitor, as adjuvant therapy for individuals with moderate persistent asthma, it would be necessary to ensure that all of the subjects were also on an anti-inflammatory agent. Alternatively, it would be ethical for an add-on study to compare an ICS against placebo for children with moderate persistent asthma provided that all the subjects were on cromolyn. Ten of the 42 placebo-controlled studies were designed as "add-on" studies. Unfortunately, 7 of the 10 studies did not ensure that all of the subjects were receiving an anti-inflammatory agent (standard of care) at study enrollment. Although the subjects were allowed to continue cromolyn and/or ICS, none of the studies required that all subjects take anti-inflammatory medications, and the data show that not all subjects were on them. In the other 3 studies, all the subjects were on an anti-inflammatory agent. Thus, of the 42 placebo-controlled trials, 3 had ethical methodologies.

A third way that placebo-controlled trials in asthma would be ethical is if the commonly used therapy for the condition carries with it a high frequency of unacceptable side effects. Although there were serious concerns regarding the

therapy for the period of the clinical trial is unlikely to produce any significant long-term losses for the patient; (2) the patient is aware that the therapy in question is proven to be efficacious and may be withheld as part of the trial and nevertheless agrees to participate in the trial; and (3) conducting the trial as a placebo-controlled trial rather than as an active-controlled trial produces considerable scientific gains and/or substantially lessens the cost of conducting the trial." *Id.* His position is that if these conditions are met, then "the requirements of respecting patient autonomy and of protecting patients from excessive risks are met, and the research in question would be morally licit." *Id.* One major problem with Brody's argument is that the requirements are or ought to be not merely to protect patients from excessive risks, but rather to minimize risks. This standard is found in many national and international research ethics documents. See, e.g., Nuremberg Code, Principle 4; 45 C.F.R. § 46 at Subpart A, 46.111(a)(1); MEDICAL RES. COUNCIL OF CANADA, NATURAL SCI. AND ENGINEERING RES. COUNCIL OF CANADA, SOCIAL SCI. AND HUMANITIES RES. COUNCIL OF CANADA, TRI-COUNCIL POL'Y STATEMENT: ETHICAL CONDUCT FOR RES. INVOLVING HUM. 1.6 (1998) (last visited September 14, 2002), available at <http://www.nserc.ca/programs/ethics/english/policy.htm>; NAT'L COMM'N, *supra* note 8, at 2. It is also not clear whether Brody would want his argument to be used for pediatric research where the emphasis on autonomy is of less significance and the role of protection is and ought to be much more stringent. See LAINIE FRIEDMAN ROSS, CHILDREN, FAMILIES, AND HEALTH CARE DECISION MAKING 89-93 (1998).

99. Gail Shapiro et al., *Efficacy and Safety of Budesonide Inhalation Suspension (Pulmicort Respules) in Young Children with Inhaled Steroid-Dependent, Persistent Asthma*, 102 J. ALLERGY & CLINICAL IMMUNOLOGY 789, 795 (1998).

potential side effects of ICS, it is fair to say that by the early 1990s, most of these had been disproven,¹⁰⁰ even though research continues to look for long-term side effects.

The final two justifications for a placebo-controlled trial are if the commonly used therapy for the condition is of questionable or low efficacy (condition 3), and if the disease process is characterized by frequent spontaneous exacerbations and remissions (condition 5). These conditions do not apply to the treatment of moderate to severe asthma in the 1990s.

What, then, do our data show? From an ethics perspective, our data show that current placebo-controlled asthma trials are methodologically flawed. First, they lack clinical equipoise. The researchers expect the patient-subjects on placebo to do worse than those on the experimental ICS. Second, they fail to provide all subjects in the control arm with current standard of care. Clearly, this is the case in any study involving individuals with more than mild intermittent asthma who receive a placebo instead of an anti-inflammatory agent. Even those studies that test experimental drugs as add-ons fail to ensure that all of the patient-subjects are receiving an anti-inflammatory agent (standard of care) at the time the new drug is added on to their medical regimen. The result is, not surprisingly, that subjects who receive placebo withdraw more frequently and have more frequent asthma exacerbations.¹⁰¹ These children are also being placed at risk for chronic irreversible changes.¹⁰²

The studies are also not scientifically valid. Miller and Shorr recently published an in-depth analysis of a "typical" placebo-controlled asthma study.¹⁰³ The study they analyzed compared mometasone furoate (MF), an ICS, at two different doses versus beclomethasone dipropionate (BDP), another ICS, versus

100. Brogden, *supra* note 85, at 117-19; Clissold & Heel, *supra* note 80, at 511.

101. Coffey, *supra* note 92. The issue of harm in placebo-controlled asthma trials is further developed by M. Justin Coffey, Benjamin Wilfond & Lainie Friedman Ross, *The Ethics of Placebo-Controlled Asthma Studies Enrolling Children* (2002) (manuscript in review, on file with author) [hereinafter Coffey et al.].

102. This danger was noted by one group of researchers who explained why they specifically chose not to do a double-blind study, even if the design would be criticized as "a double-blind treatment protocol would have required that patients treated only with an inhaled beta-2-agonist would have had to be given a placebo for the inhaled corticosteroid for up to 2 years and then switched to the active corticosteroid treatment phase for an equally long period of time. The other group should have had active treatment with the inhaled corticosteroid from the beginning. With our current understanding of asthma as an inflammatory disease, such a study would certainly be considered unethical . . ." See also Olof Selroos et al., *Effect of Early vs. Late Intervention with Inhaled Corticosteroids in Asthma*, 108 CHEST 1228, 1233 (1995). The risk of irreversible damage has been shown in several studies. See, e.g., L. Agertoft & Søren Pedersen, *Effects of Long-Term Treatment with an Inhaled Corticosteroid on Growth and Pulmonary Function in Asthmatic Children*, 88 RESPIRATORY MED. 373 (1994); Tari Haastela et al., *Effects of Reducing or Discontinuing Inhaled Budesonide in Patients with Mild Asthma*, 331 NEW ENG. J. MED. 700 (1994).

103. Franklin G. Miller & Andrew F. Shorr, *Ethical Assessment of Industry-Sponsored Clinical Trials: A Case Analysis*, 121 CHEST 1337 (2002).

placebo in subjects with moderate persistent asthma.¹⁰⁴ Miller and Shorr note that the researchers did not articulate a specific scientific question to be answered by the trial, but that the researchers noted that MF has been found to be well-tolerated and efficacious in previous studies.¹⁰⁵ They argue that: "In view of the already demonstrated efficacy of MF in the treatment of persistent asthma, the scientific value of another trial designed to test the efficacy of MF as compared with placebo is dubious."¹⁰⁶ Rather, they argue, "testing the equivalence or superiority of MF . . . to BDP would have been scientifically and clinically valuable."¹⁰⁷ If further testing of efficacy was unnecessary at the time of the study, then the study itself is not ethical as one of the fundamental principles for research to be ethical is that the study is scientifically sound; otherwise, one cannot justify placing any human subjects at any risk.¹⁰⁸

VII. STUDIES INVOLVING CHILDREN AND ADULTS

Of the 57 asthma studies, 41 included children and adults. In fact, the number of studies with children and adults was 8 (of 15) in 1998, 19 (of 23) in 1999, and 14 (of 19) in 2000. The increasing percentage of studies that include adolescents and adults may reflect the changing attitude toward the participation of children that was being expressed in the mid-1990s, although it cannot be asserted as most of the studies do not state when enrollment began.¹⁰⁹

What is the purpose of enrolling children, a vulnerable population, in clinical research? According to the National Commission's report on research involving children, the purpose should be to enhance the well-being of children generally.¹¹⁰ As such, one would assume that any clinical drug trial that enrolled children would have as one of its goals an assessment of the safety and efficacy of the drug on

104. See generally Robert A. Nathan et al., *Mometasone Furoate: Efficacy and Safety in Moderate Asthma Compared with Beclomethasone Dipropionate*, 86 ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY 203 (2001). This study was published after 2000 and is not included in our analysis. We are however, continuing this study beyond data from 2000. Coffey et al., *supra* note 101.

105. Miller & Shorr, *supra* note 103, at 1338.

106. Miller & Shorr, *supra* note 103, at 1338.

107. Miller & Shorr, *supra* note 103, at 1338.

108. See, e.g., Nuremberg Code, *supra* note 22, principles 2, 3, & 6; WORLD MED. ASS'N, *supra* note 23, principles 1, 5, & 6.

109. In 1995, the standards for reporting clinical trials were developed by an international group of clinical trialists, statisticians, epidemiologists, and biomedical editors. See Colin Begg et al., *Improving the Quality of Reporting of Randomized Controlled Trials: The CONSORT Statement*, 276 JAMA 637 (1996). The standards, known as CONSORT (Consolidated Standards of Reporting Trials) have been widely accepted and many journals refer potential authors to them. Although CONSORT require researchers to describe when and how the study was done, these data were often missing from the studies we reviewed. Of note, CONSORT has been revised in 2001. See David Moher et al., *The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials*, 357 LANCET 1191, 1194 (2001).

110. NAT'L COMM'N, *supra* note 8, at 1-2.

children. Unfortunately, only one of the 41 studies that included children and adults did subset analysis to determine 1) if the treatment responses in children were the same or different than the responses in adults; or 2) whether the adverse events and withdrawals occurred more frequently in the pediatric subjects or in the adult subjects.¹¹¹

In response to two asthma studies that included subjects older than 12 years and were published in the same issue of *JAMA* in 2001,¹¹² one of us (LFR) questioned the authors regarding the reason for including children if not enough subjects would be enrolled to make useful subset analyses.¹¹³ While Lazarus agreed that “studies involving children must balance the generalizability of results against the risk of participation,”¹¹⁴ Lemanske responded that “neither trial was designed specifically to evaluate if the response of children or adolescents differed from adults; rather patient selection was based on criteria that would permit the results to be generalized to the patient populations for which these medications were approved by the FDA and routinely prescribed.”¹¹⁵ Given the lack of pediatric data, it is unclear what benefit there is to the enrollment of children. While it may help the researchers achieve their enrollment criteria more quickly, the participation of adolescents is not permissible under the federal guidelines which require that the risk/benefit balance be favorable for the adolescents who participate.¹¹⁶

If clinical drug trials that enroll children do not benefit children as a class, the children-subjects in all arms of the study should at least be assured standard of care. Unfortunately, 34 of the 41 studies including children and adults do not ensure that all subjects are receiving anti-inflammatory medication (standard of care) throughout the trial. In fact, 26 of these studies deny some subjects anti-inflammatory medication by enrolling them in a placebo arm. As such, our analysis of the research that enrolled children and adults indicates that the research provides neither individual nor class benefits, and supports our preference for a “children last” policy.

111. Donald P. Tashkin et al., *An Evaluation of Zafirlukast in the Treatment of Asthma with Exploratory Subset Analyses*, 103 J. ALLERGY & CLINICAL IMMUNOLOGY 246, 249 (1999).

112. See generally Stephen C. Lazarus et al., *Long-Acting Beta-2-Agonist Monotherapy vs. Continued Therapy with Inhaled Corticosteroids in Patients with Persistent Asthma: A Randomized Controlled Trial*, 285 JAMA 2583 (2001); Robert F. Lemanske Jr. et al., *Inhaled Corticosteroid Reduction and Elimination in Patients with Persistent Asthma Receiving Salmeterol: A Randomized Clinical Trial*, 285 JAMA 2594 (2001).

113. Letter from Lainie Friedman Ross to Editor, *in JAMA*, 286 JAMA 3075, 3076 (2001).

114. Letter from Stephen C. Lazarus to Editor, *in JAMA*, 286 JAMA 3075, 3077 (2001).

115. Robert F. Lemanske, Jr., *In Reply, Salmeterol and Inhaled Corticosteroids in Patients with Persistent Asthma*, 286 JAMA 3078, 3078 (2001).

116. The study by Lazarus failed to provide all subjects with ICS and clearly placed some subjects at unnecessary risk. Friedman letter, *supra* note 114. The study by Lemanske was not problematic methodologically, but it is unclear why adolescents were involved if there was no plan to get information that would advance the well-being of children generally. Lazarus, *supra* note 115.

VIII. WHY SUCH RESEARCH DESIGNS?

It should be clear, then, that very few of the asthma studies published between 1998 and 2000 were done ethically, despite the fact that 54 of the 57 reported IRB review and 55 of the 57 reported that consent was procured. One could argue that the research was ethical because the subjects and/or their parents knew the aim of the research and its methodology and were free to consent or to refuse to consent to participate. Such an argument, however, fails to acknowledge the dual responsibility of IRBs: both to ensure patient-subject autonomy and to protect human subjects.¹¹⁷ Consent is necessary, but not sufficient. Rather, the protection of human subjects also requires that the research risks be minimized.¹¹⁸

Why then did the researchers choose such study designs? We believe, as Shapiro explained in her response to Ferdman and Church's letter, that some of the research is being done to get compelling data to garner FDA-approval. Although the FDA does not require placebo-controlled studies, it is clear that the FDA favors them.¹¹⁹

Other researchers use placebo-controlled trials to be able to show significant results. Many of the review articles to date show that the differences in efficacy and side effects of the different ICS are not clinically significant.¹²⁰ Thus, any trial that compares an ICS against placebo shows greater differences than a trial that compares one ICS against a competitor ICS. To that extent, the research functions more as medical advertisement to increase market share than as groundbreaking research.¹²¹

117. NAT'L COMM'N FOR THE PROTECTION OF HUM. SUBJECTS OF BIOMEDICAL AND BEHAV. RES., PUB. NO. (OS) 78-0008, 78-0009, 1-2 *REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS* (1978).

118. Nuremberg Code, *supra* note 22; WORLD MED. ASS'N, *supra* note 23.

119. Brody does an extensive analysis of the FDA and its position regarding studies that use placebos versus active controls. See BRODY, *supra* note 57, at 105-16.

120. See Pedersen & O'Byrne, *supra* note 84, at 28-29 (arguing that the methodologies of many of the studies do not allow a firm conclusion to be made about the relative advantages and disadvantages of the ICS). Other factors can influence the efficacy of inhaled corticosteroids besides the compound and the dose including the devices used to deliver the drugs. There has been much research on different types of drug-delivery devices and propellants, in part, because the older formulations of ICS used chlorofluorocarbon (CFC) propellants that are now banned because of their harmful effect on the environment. Drug manufacturers have solved this issue by using either finely divided dry powders or by substituting a non-CFC propellant, both of which may be better for patients than the CFC-metered dose inhalers. See, e.g., Philip S. Norman, Johns Hopkins University Asthma and Allergy News, *New Ways to Formulate Inhaled or Sprayed Drugs*, available at <http://www.hopkins-allergy.org/news/articles/1999/102899.html> (last visited September 18, 2002). It is worth noting that none of the guidelines prefer one ICS to another. In the NAEPP 1997 guidelines, estimated comparative daily dosages for inhaled corticosteroids are given. NHLBI, *supra* note 76, at 88-90 (figures 3-5b and 3-5c).

121. See, e.g., Gary B. Weiss & William J. Winslade, *Is Post-Marketing Drug Follow-Up Research or Advertising?*, 9 IRB: REV. HUM. SUBJECTS RES. 10 (1987).

Many of the ICS placebo-controlled studies published between 1998 and 2000 replicate results. Consider, for example, a paper by Baker et al. published in 1999 comparing budesonide inhalation suspension (BIS), an ICS, and placebo in 480 infants and children with asthma. The researchers noted that their results are similar to the findings of nine other studies that evaluated the efficacy of BIS in young children with asthma.¹²² The numerous replications of asthma trials contrast sharply with the paucity of research done to replicate efficacy of innovative therapies lacking commercial value.¹²³ What distinguishes the asthma trials from these examples is that the former studies are being funded by pharmaceutical companies who have a financial interest in completing these studies.¹²⁴ Often these studies are not being done primarily to promote or advance asthma care, but to get "me-too" drugs to market or to increase the brand's market share.

One may argue that we are being too harsh. There is a need to replicate research results in order to ensure that the findings are correct and do not reflect a statistical anomaly. We agree. But before one can justify additional placebo-controlled asthma trials, one should examine the world literature. Many of the studies examining the efficacy of ICS against placebo between 1998 and 2000 merely duplicate research already performed by European researchers and published in the European literature.¹²⁵

Finally, we do not mean to suggest that all pharmaceutically funded research is unethical. However, our case study supports the position that the source of funding changes what is studied,¹²⁶ how it is studied,¹²⁷ and what is published.¹²⁸

122. James W. Baker et al., *A Multiple-Dosing, Placebo-Controlled Study of Budesonide Inhalation Suspension Given Once or Twice Daily for Treatment of Persistent Asthma in Young Children and Infants*, 103 PEDIATRICS 414, 418 (1999).

123. See William A. Silverman, *Non-replication of the Replicable*, 10 PEDIATRIC & PERINATAL EPIDEMIOLOGY 406 (1996), in WILLIAM A. SILVERMAN, WHERE'S THE EVIDENCE? DEBATES IN MODERN MEDICINE 163-66 (1998). See generally Andrew Haines & Roger Jones, *Implementing Findings of Research*, 308 BRIT. MED. J. 1488 (1994).

124. Of the 57 studies, two did not report the funding source. Of the remainder, 55 (92%) were pharmaceutically funded, one was NIH funded (with drugs supplied by the pharmaceutical companies), and one was institutionally funded. Coffey, *supra* note 101, at 24.

125. Consider, for example, that a review of budesonide in 1984 reported dozens of therapeutic studies, both short and long term trials, in children and in adults, using both active and placebo controls, at various dosages and time intervals. Clissold & Heel, *supra* note 80, at 499-506. Likewise, a review of fluticasone propionate in 2000 reported dozens of studies involving more than 3,000 subjects prior to 1994. Again, these studies included both active and placebo controls. Stephen M. Holliday et al., *Inhaled Fluticasone Propionate: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Asthma*, 47 DRUGS 318, 325-27 (1994). Six of our 57 studies examined the efficacy of budesonide; 18 examined fluticasone propionate. *Id.*

126. See discussion *supra*, accompanying notes 120-25.

127. Bodenheimer discusses the recent move away from academic medical centers as the "sole citadels of clinical research." Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1539 (2000). Rather, in the last 10 years there has been a shift towards commercially oriented networks of contract-research organizations (CROs) and site-management organizations (SMOs). Djulbegovic also notes that industry-sponsored studies are

The implications are particularly significant because pharmaceutical spending currently accounts for over 50% of funding of clinical trials of new drugs.¹²⁹

IX. CONCLUDING REMARKS

The recent policy initiatives for children as research subjects place too much emphasis on access and leave children at risk of being exposed to unnecessary harm. We have utilized U.S. based asthma research to support this concern.

Children are a vulnerable population in clinical research and need additional protection. This means that we should maintain the former recommendations of the National Commission to perform research first on animals, second on adults, and only then on children. It also means that when we do involve children, we should do so in a way that benefits children as a class. Lifeboat ethics is not the appropriate model for human experimentation on children. The ideological shift from a focus on protection to a focus on access has exposed children to unnecessary risk.

more likely to be designed to compare experimental treatment against placebo or no therapy than did studies sponsored by public resources. See generally Benjamin Djulbegovic et al., *The Uncertainty Principle and Industry-Sponsored Research*, 356 LANCET 635 (2000).

128. Davidson found that few trials supported by pharmaceutical manufacturers favor traditional therapy, although some reasons may be legitimate (e.g., the selection of drugs for study that are likely to be proven efficacious). However, it may also reflect a decision not to publish negative results. See Richard A. Davidson, *Source of Funding and Outcome of Clinical Trials*, 1 J. GEN. INTERNAL MED. 155, 156-57 (1986).

129. In 2001, federal spending on biomedical science was slightly more than \$20 billion, whereas drug companies spent \$22.4 billion in 2000. Robert Lee Hotz, *Science File: Scientists Sharing Fewer Discoveries*, L.A. TIMES, Feb. 11, 2002, available at 2002 WL 2453012. Biomedical research is also sponsored to a lesser extent by not-for-profit philanthropies. *Id.*